CLAIMS

1. A method for screening, diagnosis or prognosis of hepatoma in a human subject for determining the stage or severity of hepatoma in a subject, for identifying a subject at risk of developing hepatoma, or for monitoring the effect of therapy administered to a subject having hepatoma, said method comprising:

(a) analyzing a test sample of body fluid from the subject by two-dimensional electrophoresis to generate a two-dimensional array of features, said array comprising at least one chosen Hepatoma-Diagnostic Feature (HF) selected from: HF-1, HF-2, HF-3, HF-4, HF-5, HF-6, HF-7, HF-8, HF-9, HF-10, HF-11, HF-12, HF-13, HF-14, HF-15, HF-16, HF-17, HF-18, HF-19, HF-20, HF-21, HF-22, HF-23, HF-24, HF-25, HF-26, HF-27, HF-28, HF-29, HF-30, HF-31, HF-32, HF-33, HF-34, HF-35, HF-36, HF-37, HF-38, HF-39, HF-40, HF-41, HF-42, HF-43, HF-44, HF-45, HF-46, HF-47, HF-48, HF-49, HF-50, HF-51, HF-52, HF-53, HF-54, HF-55, HF-56, HF-57, HF-58, HF-59, HF-60, HF-61, HF-62, HF-63, HF-64, HF-65, HF-66, HF-67, HF-68, HF-69, HF-70, HF-71, HF-72, HF-73, HF-74, HF-75, HF-76, HF-77, HF-78, HF-79, HF-80, HF-81, HF-82, HF-83, HF-84, HF-85, HF-86, HF-87, HF-88, HF-89, HF-90, HF-91, HF-92, HF-93, HF-94, HF-95, HF-96, HF-97, HF-98, HF-99, HF-100, HF-101, HF-102, HF-103, HF-104, HF-105, HF-106, HF-107, HF-108, HF-109, HF-110, HF-111, HF-112, HF-113, HF-114, HF-115, HF-116, HF-117, HF-118, HF-119, HF-120, HF-121, HF-122, HF-123, HF-124, HF-125, HF-126, HF-127, HF-128, HF-129, HF-130, HF-131, HF-132, HF-133, HF-134, HF-135, HF-136, HF-137, HF-138, HF-139, HF-140, HF-141; and

(b) comparing the abundance of each chosen feature in the test sample with the abundance of that chosen feature in body fluid from one or more persons free from hepatoma, or with a previously determined reference range for that feature in subjects free from hepatoma, or with the abundance at least one Expression Reference Feature (ERF) in the test sample.

2. The method according to claim 1, wherein step (a) comprises quantitatively detecting at least one of the following HFs: HF-1, HF-3, HF-10, HF-15, HF-16, HF-17, HF-18, HF-19, HF-20, HF-21, HF-23, HF-24, HF-25, HF-26, HF-28, HF-29, HF-31, HF-32, HF-33, HF-34, HF-36, HF-37, HF-38, HF-39, HF-40, HF-42, HF-44, HF-46, HF-47, HF-48, HF-49, HF-51, HF-52, HF-53, HF-54, HF-55, HF-56, HF-59, HF-60, HF-63, HF-75, HF-84, HF-85, HF-89, HF-91, HF-97, HF-100, HF-103, HF-109, HF-110, HF-112, HF-113, HF-120, HF-121, HF-122 and HF-124.

3. The method according to claim 2, wherein step (a) comprises quantitatively detecting at least one of the following HFs: HF-17, HF-18, HF-20, HF-23, HF-24, HF-25, HF-29, HF-33, HF-34, HF-39, HF-44, HF-55, HF-60, HF-75, HF-84, HF-85, HF-89, HF-91, HF-97, HF-110, HF-113, HF-120, HF-121, HF-122 and HF-124.

4. The method according to any one of claims 1 to 3, wherein the body fluid is serum or plasma.

5. The method according to claim 1, wherein step (b) comprises comparing the abundance of each chosen feature in the sample with the abundance of that chosen feature in serum or plasma from one or more persons free from hepatoma or with a previously determined reference range for that chosen feature in subjects free from hepatoma.

6. The method as claimed in claim 1, which is used in combination with an assay or assessment for Hepatitis B and/or Hepatitis C.

7. A method for screening, diagnosis or prognosis of hepatoma in a subject, for determining the stage or severity of hepatoma in a subject, for identifying a subject at risk of developing hepatoma, or for monitoring the effect of therapy administered to a subject having hepataoma, said method comprising quantitatively detecting, in a sample of serum or plasma from the subject, at least one of the following Hepatoma-Diagnostic Protein Isoforms (HPIs): HPI-1, HPI-2, HPI-3, HPI-4, HPI-5, HPI-6, HPI-8, HPI-9, HPI-10, HPI-11, HPI-12, HPI-13, HPI-14, HPI-15, HPI-16, HPI-17, HPI-18, HPI-19, HPI-20, HPI-21, HPI-22, HPI-23, HPI-24, HPI-25, HPI-26 and HPI-27.

8. The method according to claim 7, wherein the step of quantitatively detecting comprises testing at least one aliquot of the sample, said step of testing comprising:

(a) contacting the aliquot with an antibody that is immunospecific for a preselected HPI; and

(b) detecting whether binding has occurred between the antibody and at least one species in the aliquot.

9. The method according to claim 8, wherein the step of quantitatively detecting comprises testing a plurality of aliquots with a plurality of antibodies for quantitative detection of a plurality of preselected HPIs.

10. An antibody capable of immunospecific binding to one of the following Hepatoma-Diagnostic Protein Isoforms (HPIs): HPI-1, HPI-2, HPI-3, HPI-4, HPI-5, HPI-6, HPI-8, HPI-9, HPI-10, HPI-11, HPI-12, HPI-13, HPI-14, HPI-15, HPI-16, HPI-17, HPI-18, HPI-19, HPI-20, HPI-21, HPI-22, HPI-23, HPI-24, HPI-25, HPI-26 and HPI-27.

11. The antibody of claim 10, which is selected from monoclonal antibodies, chimeric antibodies, humanized antibodies and bispecific antibodies.

12. A preparation comprising at least one of the following isolated Hepatoma-Diagnostic Protein Isoforms (HPIs): HPI-1, HPI-2, HPI-3, HPI-4, HPI-5, HPI-6, HPI-8, HPI-9, HPI-10, HPI-11, HPI-12, HPI-13, HPI-14, HPI-15, HPI-16, HPI-17, HPI-18, HPI-19, HPI-20, HPI-21, HPI-22, HPI-23, HPI-24, HPI-25, HPI-26 and HPI-27 or an antibody or a fragment or derivative of an antibody as claimed in claim 10, said fragment or derivative containing the binding domain of the antibody as claimed in claims 10, optionally with a pharmaceutically acceptable carrier.

13. A method of treating or preventing hepatoma comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of an antibody or a fragment or derivative of an antibody as claimed in claim 10, said fragment or derivative containing the binding domain of the antibody as claimed in claim 10 to 14.

14. The method of claim 13, wherein the antibody is used as a vaccine.

15. A method of treating or preventing hepatoma comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of a nucleic acid encoding one of the following Hepatoma-Diagnostic Protein Isoforms (HPIs): HPI-1, HPI-2, HPI-3, HPI-4, HPI-5, HPI-6, HPI-8, HPI-9, HPI-10, HPI-11,

HPI-12, HPI-13, HPI-14, HPI-15, HPI-16, HPI-17, HPI-18, HPI-19, HPI-20, HPI-21, HPI-22, HPI-23, HPI-24, HPI-25, HPI-26 and HPI-27.

16. A method of treating or preventing hepatoma comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of a nucleic acid that inhibits the expression or function of one or more of the following Hepatoma-Diagnostic Protein Isoforms (HPIs): HPI-1, HPI-2, HPI-3, HPI-4, HPI-5, HPI-6, HPI-8, HPI-9, HPI-10, HPI-11, HPI-12, HPI-13, HPI-14, HPI-15, HPI-16, HPI-17, HPI-18, HPI-19, HPI-20, HPI-21, HPI-22, HPI-23, HPI-24, HPI-25, HPI-26 and HPI-27.

17. The method of claim 16, wherein the nucleic acid is a HPI antisense nucleic acid or ribozyme.

18. A method of screening for agents that interact with a Hepatoma-Diagnostic Protein Isoform (HPI), selected from HPI-1, HPI-2, HPI-3, HPI-4, HPI-5, HPI-6, HPI-8, HPI-9, HPI-10, HPI-11, HPI-12, HPI-13, HPI-14, HPI-15, HPI-16, HPI-17, HPI-18, HPI-19, HPI-20, HPI-21, HPI-22, HPI-23, HPI-24, HPI-25, HPI-26 and HPI-27, or a HPI fragment, or HPI-related polypeptide said method comprising:

(a) contacting a HPI, a HPI fragment, or a HPI-related polypeptide with a candidate agent; and

(b) determining whether or not the candidate agent interacts with the HPI, the HPI fragment, or the HPI-related polypeptide.

19. A method of screening for agents that modulate the expression or activity of a Hepatoma-Diagnostic Protein Isoform (HPI), selected from: HPI-1, HPI-2, HPI-3, HPI-4, HPI-5, HPI-6, HPI-8, HPI-9, HPI-10, HPI-11, HPI-12, HPI-13, HPI-14, HPI-15, HPI-16, HPI-17, HPI-18, HPI-19, HPI-20, HPI-21, HPI-22, HPI-23, HPI-24, HPI-25, HPI-26 and HPI-27, an HPI fragment, or an HPI-related polypeptide comprising:

(a) contacting a first population of cells expressing a HPI, a HPI fragment, or a HPI-related polypeptide with a candidate agent;

(b) contacting a second population of cells expressing said HPI, said HPI fragment, or said HPI-related polypeptide with a control agent; and

(c) comparing the level of said HPI, said HPI fragment, or said HPI-related polypeptide or mRNA encoding said HPI, said HPI fragment, or said HPI-related polypeptide in the first and second populations of cells, or comparing

the level of induction of a cellular second messenger in the first and second populations of cells.

20. A method of screening for or identifying agents that modulate the expression or activity of a Hepatoma-Diagnostic Protein Isoform (HPI), selected from: HPI-1, HPI-2, HPI-3, HPI-4, HPI-5, HPI-6, HPI-8, HPI-9, HPI-10, HPI-11, HPI-12, HPI-13, HPI-14, HPI-15, HPI-16, HPI-17, HPI-18, HPI-19, HPI-20, HPI-21, HPI-22, HPI-23, HPI-24, HPI-25, HPI-26 and HPI-27, an HPI fragment, or a HPI-related polypeptide comprising:

(a) administering a candidate agent to a first mammal or group of mammals;

(b) administering a control agent to a second mammal or group of mammals; and

(c) comparing the level of expression of the HPI, the HPI fragment, or the HPI-related polypeptide or of mRNA encoding the HPI, the HPI fragment, or the HPI-related polypeptide in the first and second groups, or comparing the level of induction of a cellular second messenger in the first and second groups; and

(d) optionally comparing the levels of expression of the HPI or the HPI-related polypeptide or of mRNA encoding the HPI or the HPI-related polypeptide in the first and second groups to the level of the HPI or the HPI-related polypeptide or of mRNA encoding the HPI or the HPI-related polypeptide in normal control mammals, or comparing the level of induction of a cellular second messenger in the first and second groups, to the level of induction of a cellular second messenger in normal control mammals.

21. The method of claim 20, wherein the mammals are animal models for hepatoma or human subjects having hepatoma.

22. A method of screening for or identifying agents that modulate the activity of a Hepatoma-Diagnostic Protein Isoform (HPI), selected from: HPI-1, HPI-2, HPI-3, HPI-4, HPI-5, HPI-6, HPI-8, HPI-9, HPI-10, HPI-11, HPI-12, HPI-13, HPI-14, HPI-15, HPI-16, HPI-17, HPI-18, HPI-19, HPI-20, HPI-21, HPI-22, HPI-23, HPI-24, HPI-25, HPI-26 and HPI-27, an HPI fragment, or a HPI-related polypeptide, comprising

(a) in a first aliquot, contacting a candidate agent with the HPI, the HPI fragment, or the HPI-related polypeptide, and

(b) comparing the activity of the HPI, the HPI fragment, or the HPI-related polypeptide in the first aliquot after addition of the candidate agent with the activity of the HPI, the HPI fragment, or the HPI-related polypeptide in a control aliquot, or with a previously determined reference range.

23. The method according to claim 22, wherein the HPI, the HPI fragment, or the HPI-related polypeptide is recombinant protein.

24. The method according to claim 22, wherein the HPI, the HPI fragment, or the HPI-related polypeptide is immobilized on a solid phase.

25. An isolated nucleic acid molecule that hybridizes to a nucleotide sequence encoding HPI-13 or HPI-21 or their complements.

26. An isolated nucleic acid molecule that hybridizes to a nucleotide sequence encoding at least 10 consecutive amino acids of HPI-13 or HPI-21 or their complements.

27. A vector comprising the nucleic acid molecule of claim 25.

28. A host cell comprising the vector of claim 27.

29. A host cell genetically engineered to express the nucleic acid molecule of claim 25.

30. A method for screening, diagnosis or prognosis of hepatoma in a subject or for monitoring the effect of an anti-hepatoma drug or therapy administered to a subject, comprising:

(a) contacting at least one oligonucleotide probe comprising 10 or more consecutive nucleotides complementary to a nucleotide sequence encoding a HPI chosen from HPI-1, HPI-2, HPI-3, HPI-4, HPI-5, HPI-6, HPI-8, HPI-9, HPI-10, HPI-11, HPI-12, HPI-13, HPI-14, HPI-15, HPI-16, HPI-17, HPI-18, HPI-19, HPI-20, HPI-21, HPI-22, HPI-23, HPI-24, HPI-25, HPI-26 and HPI-27 with an RNA obtained from a biological sample from the subject or with cDNA copied from the RNA wherein said contacting occurs under conditions that permit hybridization of the probe to the nucleotide sequence if present;

(b) detecting hybridization, if any, between the probe and the nucleotide sequence; and

(c) comparing the hybridization, if any, detected in step (b) with the hybridization detected in a control sample, or with a previously determined reference range.

31. The method of claim 30, wherein step (a) includes the step of hybridizing the nucleotide sequence to a DNA array, wherein one or more members of the array are the probes complementary to a plurality of nucleotide sequences encoding distinct HPIs.